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A protocol to accomplish 'homo-Robinson' annulation: application to the guanacastepene problem

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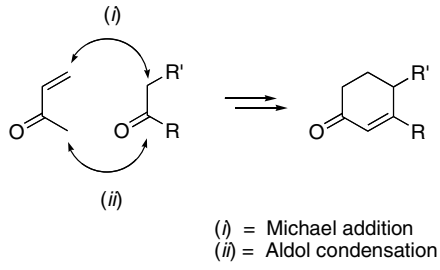
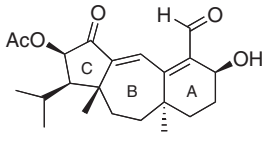
Dedicated with admiration to Professor Eun Lee on the occasion of his 60th birthday in recognition of his many contributions to chemistry and chemical education

Abstract—A sequence which accomplishes the preparation of cycloheptadienones by ring-expansion of fused cyclohexenones has been developed and applied to the improved synthesis of a key intermediate in the total synthesis of guanacastepene A.

The Robinson annulation has been of major value in organic synthesis since its introduction many years ago.[1,2] Many tactical variants are known.[3] However, globally, the overall sequence is comprised of Michael addition of an enol or enolate to an α,β-unsaturated ketone. The addition step is coordinated with intramolecular aldol condensation and dehydration, to produce a cyclohexenone ring.



As part of our continuing synthetic interest in the guanacastepenes (Scheme 1),[4–6] we came to consider possible extensions of the original Robinson annulation with a view to synthesizing its B,C system, originally in the form of hydroazulenone structure **3** (Scheme 2). To this end, we hoped to reach **3** by intramolecular Horner–Wadsworth–Emmons cyclization of **2**. In the event, a cyclization did occur; however, the desired hydroazulenone **3** was not observed. Thus, when treated with 5.0 equiv of Cs_2CO_3 in refluxing toluene, compound **2** was converted to a single product, identified as the fused cyclopentenone **4**.[5a] Indeed, Snider and Hawryluk had also observed only the formation of compound **4** following treatment of the methyl ketone **5** with base.[6a] Fortunately for the unfolding of our total synthesis, a viable and concise reductive cyclization[7]-oxidative rearrangement[8] sequence, which led from **6** to the target substructure **3**, was developed.[5a]



Guanacastepene A (**1**)

Scheme 1. Structure of guanacastepene A (**1**).

Thus, our ability to reach guanacastepene A did serve to establish compound **3** as a productive total synthesis intermediate.[5d,e] Being well aware of a competitive reductive but non-cyclizing pathway (see **6** → **7**), which complicated our original route to **3** via **6**, we returned

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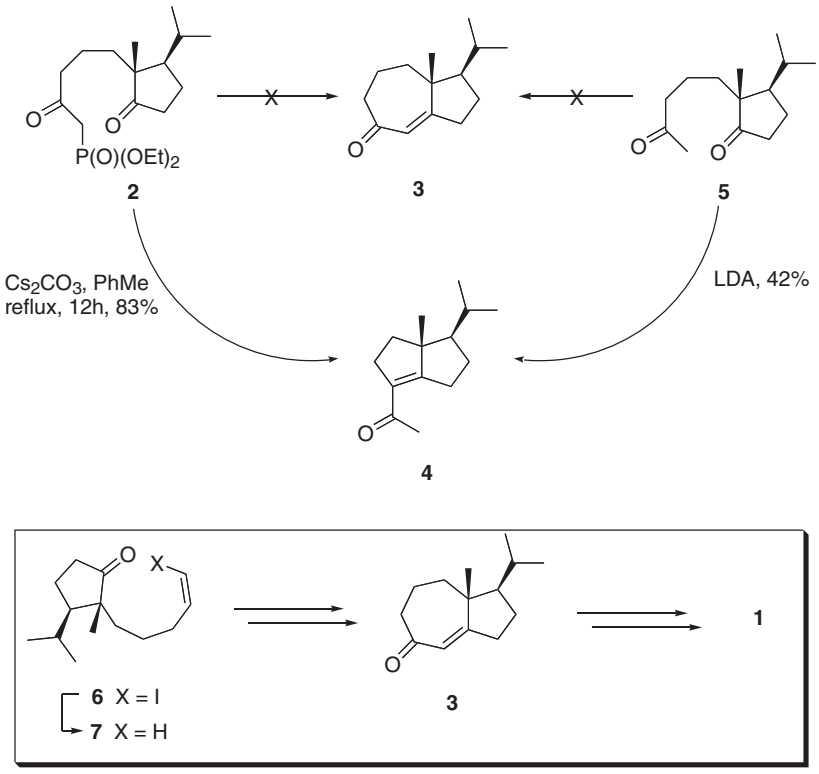
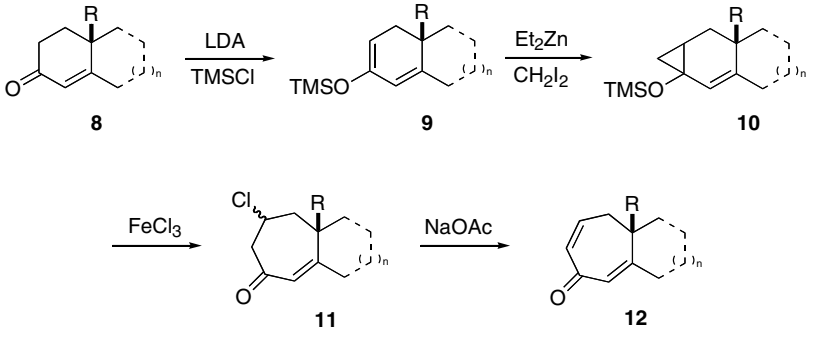


Scheme 2. Unsuccessful Robinson annulation strategies to construct hydroazulene core.

to the problem of synthesizing fused cycloheptenones. Given the experiences in attempted direct intramolecular aldol-like closures to type **3** structures described above (**2** and **5** → **4**),[9] we investigated an alternate possibility, i.e., that of directed ring expansion of a fused cyclohexenone. In this approach, we would be taking full advantage of the formidable body of prior art implied in the first figure to provide our matrix cyclohexenones. In particular, we were drawn to earlier work of Saegusa involving oxidative cleavage of silyloxycyclopropanes.[10] His protocol draws upon a four-step sequence which culminates in a homologous α,β-unsaturated ketone via a one-carbon expansion of a cycloalkenone. As a model reaction, Saegusa had shown that a 1-silyloxybicyclo[4.1.0]heptane can be converted efficiently to a 2-cycloheptenone under oxidative mediation by $FeCl_3$.

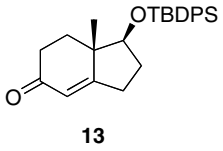
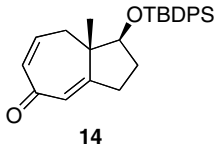
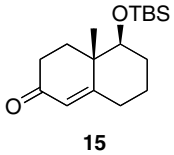
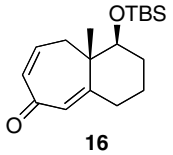
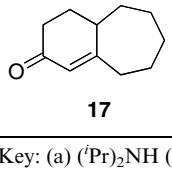
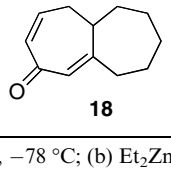
Accordingly, we investigated the applicability of the Saegusa ring expansion strategy to the case of a fused cyclohexenone substrate, hoping to reach a fused cycloheptenone (cf. **3**). A proof of principle conversion of an octalone (cf. **8**) to a silyloxyvinylcyclopropane (cf. **10**) via a cross-conjugated siloxydiene (cf. **9**) had been demonstrated. We hoped that $FeCl_3$-induced oxidative cleavage of the fused bond of the cyclopropane would occur as needed, leading to a chloroketone (cf. **11**). Following β-elimination, the cross-conjugated dienone **12** would be in hand (Scheme 3). It was assumed that selective reduction of the disubstituted double bond could be accomplished. To the best of our knowledge, application of the Saegusa ring expansion in such a context and toward such an end had not been studied.[11]

The concept discussed above has been reduced to practice. Several successful examples are summarized in Table 1. We emphasize that the protocol is implemented without purification of any intermediates.[12] Starting materials **13**[13] and **15**[14] were prepared from Hajos–



Scheme 3. Proposed route to homo-Robinson annulation products.

Table 1. Homo-Robinson strategy to construct the cycloheptadienone system

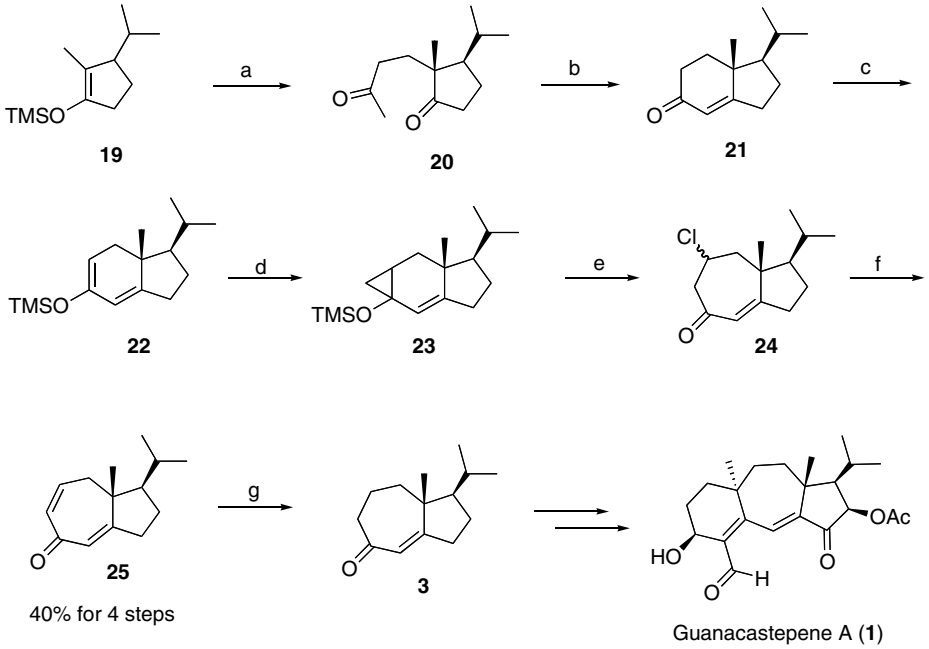
Substrate		Product	Yield (four steps)[a] (%)
 **13**	a,b → c,d	 **14**	45
 **15**	a,b → c,d	 **16**	40
 **17**	a,b → c,d	 **18**	43

[a] Key: (a) $(^{i}Pr)_2NH$ (2.5 equiv), *n*-BuLi (2.8 equiv), TMSCl (2.0 equiv), THF, −78 °C; (b) Et_2Zn (1.5 equiv), CH_2I_2 (1.1 equiv), Et_2O, 0 °C; (c) $FeCl_3$ (2.5 equiv), 0 °C; (d) NaOAc, reflux.

Parrish[15] and Wieland–Miescher[16] ketones, respectively. The previously known **17** had been prepared by a direct Robinson annulation-angular decarboxylation protocol.[17]

With these examples in hand, we next directed our attention to reaching the goal bicyclic compound **3**, a securely established intermediate in the total synthesis of guanacastepene (Scheme 4). Our synthesis commenced with the previously described compound **19**.[18] Acid-catalyzed Michael addition of the silylenol ether under a Mukayama-like protocol led to **20**.[19] Classical aldol cyclization afforded **21**. The latter was converted to the homo-annular cross-conjugated silyloxydiene **22**, which, following cyclopropanation, gave rise to **23**. Oxidative opening of **23** in the usual way, followed by dehydrohalogenation, afforded **25**. Finally, selective Wilkinson reduction[20] of **25** gave rise to the desired intermediate **3** in racemic form.[21]

We note that intermediates such as **14**, **16**, and **18**, en route to simple homo-Robinson annulation products, in principle offer incremental and exploitable functionality to differentiate sites along the cycloheptadienone moiety. In future studies, we hope to evaluate how this



Scheme 4. Formal synthesis of guanacastepene A using a homo-Robinson strategy. *Note:* Key: (a) MVK, AcOH, BF_3–Et_2O, −20 °C, 97%; (b) NaOMe, 98%; (c) $(^{i}Pr)_2NH$ (2.5 equiv), *n*-BuLi (2.8 equiv), TMSCl (2.0 equiv), THF, −78 °C; (d) Et_2Zn (1.5 equiv), CH_2I_2 (1.1 equiv), Et_2O, 0 °C; (e) $FeCl_3$ (2.5 equiv), 0 °C; (f) NaOAc, reflux, 40% yield for four steps; (g) Wilkinson's catalyst, H_2, 83%.

bonus functionality handle, which flows directly from the protocol, can be put to good use in appropriate, target-oriented synthesis contexts.

Acknowledgments

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12. General procedure: To a solution of $(^{i}Pr)_2NH$ (2.5 equiv, 2.5 mmol) in THF was added *n*-BuLi (2.8 equiv, 2.8 mmol) at −78 °C. After 30 min at 0 °C, the reaction mixture was cooled to −78 °C and a THF solution of starting cyclohexenone (1.0 equiv, 1.0 mmol) was added with stirring. After 30 min, TMSCl (2.0 equiv, 2.0 mmol) was added, the cold mixture was stirred for 30 min, then warmed to room temperature and submitted to an aqueous workup. After evaporation in vacuo, the crude diene was diluted with diethyl ether and cooled to 0 °C. Diethyl zinc (1.5 equiv, 1.5 mmol) and diiodomethane (1.1 equiv, 1.1 mmol) were successively added and the reaction mixture was warmed to room temperature. After being stirred overnight, the reaction mixture was cooled in an ice-water bath and quenched with ammonium chloride. After separation, the ether layer was filtered through a short pad of silica gel, which was washed with 20:1 (v:v) ether-pentane. The combined filtrates were washed with ammonium chloride and brine. After evaporation in vacuo, the crude trimethylsilyloxycyclopropane was diluted with DMF. To this was added, via syringe pump over 2 h, a solution of $FeCl_3$ in DMF, previously prepared by slowly adding anhydrous $FeCl_3$ (2.5 equiv, 2.5 mmol), with stirring, to DMF precooled at 0 °C. After the addition was complete, the resulting brown solution was stirred at room temperature for two more hours, then quenched with ice-cold 1 N HCl. After aqueous workup and evaporation in vacuo, the crude chlorocycloheptenone was dissolved in methanol saturated with NaOAc and heated at reflux overnight. The reaction mixture was cooled to room temperature and submitted to aqueous workup. After evaporation of organic solvent, the crude product was purified by column chromatography.
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21. Physical data for compound **3**: IR (thin film) 2956, 2870, 1652, 1464, 1426, 1366, 1336, 1260, and 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (apparent t, $J = 1.7$ Hz, 1H), 2.37–2.71 (m, 4H), 2.12 (ddd, $J = 13.9$, 7.2, and 3.5 Hz, 1H), 1.91–2.03 (m, 1H), 1.78–1.90 (m, 2H), 1.61–1.75 (m, 2H), 1.43–1.57 (m, 2H), 1.05 (s, 3H), 1.00 (d, $J = 6.7$ Hz, 3H), and 0.93 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 171.9, 123.8, 58.6, 50.0, 44.2, 38.8, 32.9, 27.9, 25.6, 24.1, 22.0, 21.0, and 20.7; HRMS Calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1666.